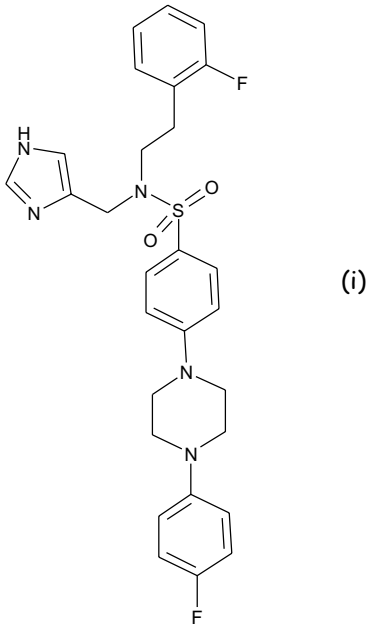
Current literature highlights – November 2001

Novel antifungals

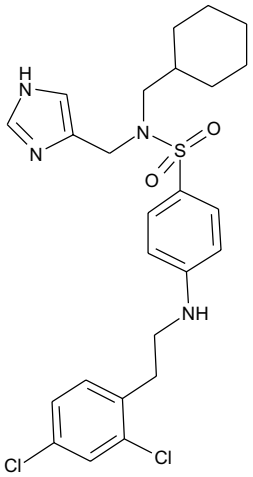
Current available therapy for treating fungal infections can suffer from drug-related toxicity, hazardous drug-drug interactions, non-optimal pharmacokinetics and the development of drug resistance. Enzymes in the ergosterol-biosynthesis pathway, specifically the lanosterol 14-α demethylase, are the targets for successful marketed antifungal drugs.

1*H*-imidazole 4-methaneamine sulphonamides are a class of imidazole-based antifungal agents which inhibit fungal ergosterol synthesis in much the same manner as triazole-containing antifungal drugs. Efforts have been made to try to understand how imidazole-based antifungal agents interact at the target enzyme via the demethylase active site. An understanding of such interaction should help in the design of more potent ergostreol synthesis inhibitors (Novel antifungals based on 4-substituted imidazole: solid-phase synthesis of substituted aryl sulfonamides towards optimisation of in vitro activity, A. K. Saha *et. al.*, Bioorg. & Med. Chem. Lett., 10, (2000), 2135-2139).

A library of 29 individual compounds, each purified by HPLC, was synthesised on 2-chlorotrityl chloride polystyrene solid phase resin. Screening of these compounds against eight isolates of *Candida* spp., revealed a number of active compounds. One of the most potent compounds discovered was (i) which possessed an IC_{50} of 3 nM against ergosterol, and 163-fold selectivity for inhibition of yeast sterol versus mammalian cholesterol synthesis. This analogue was inactive against mould strains making it uniquely yeast active. A second active compound (ii) demonstrated activity against the azole resistant strain *C. albicans* 1, and possessed an IC_{50} of 15 nM against ergosterol. This library has been successful by the continued optimisation of 4-substituted imidazole antifungals by high speed synthesis methods, leading to highly yeast-selective as well as potent broad spectrum antifungal agents. These molecules and their study may provide stimulus for further research towards the discovery of clinically successful new antifungal drugs.



(i)



(ii)

Cholesterol ester transfer protein-mRNA ligands

A number of RNA oligonucleotide/ligand interactions have been characterised and described. A 17-amino acid peptide containing the arginine-rich region of the human immunodeficiency virus (HIV) Rev protein binds to Rev response element (RRE) RNA. Also, basic peptides from the carboxy terminus of the human immunodeficiency virus type 1 (HIV-1) Tat protein bind to the stem-loop region of transactivation response region TAR RNA. This peptide that binds to TAR RNA has proven its biological activity by inhibition of HIV-1 replication in vivo.

Tripeptides that bind to the TAR RNA and inhibit gene expression could be isolated from randomised pools of combinatorial libraries (Combinatorial synthesis of cholesterol ester transfer protein mRNA ligands and screening by nodenaturating gel-electrophoresis, C. Griesinger *et. al.*, J. Med. Chem., 44, (2001), 2172-2177). A library of 625 compounds was synthesised in mixtures of 25 on an M-Mal-PEG solid phase resin. Small peptide ligands were found which bind to a 23-nt RNA oligonucleotide from the cholesterol ester transfer protein mRNA. A 27-nt RNA oligonucleotide from the human immunodeficiency virus type-1 TAR RNA was used to control the binding specificity. Gel-shift affinity screening was used to extract the peptides with the best RNA binding properties. Following deconvolution of the library, the peptide showing the most visible affinity for the 23-nt RNA was (iii) which gave a binding constant K_d of 32 μM. This work has demonstrated that it is possible to obtain peptide ligands for different RNA targets using a gel-shift assay. Also, elucidation of the minimum pharmacophoric elements requirements for binding has been achieved, namely basic and hydrophobic residues. This work lays the foundation for the design of more potent inhibitors in the future.

Lys-Tyr-Lys-Leu-Tyr-Lys-Cys-NH_2

(iii)